**UNITED STATES DISTRICT COURT**
**FOR THE SOUTHERN DISTRICT OF NEW YORK**

| | |
|---|---|
| AMARIN PHARMA, INC., *et al.*,<br><br>Plaintiffs,<br><br>v.<br><br>UNITED STATES FOOD & DRUG ADMINISTRATION; UNITED STATES OF AMERICA; STEPHEN OSTROFF, M.D., in his official capacity as Acting Commissioner of Food and Drugs; and SYLVIA MATHEWS BURWELL, in her official capacity as Secretary of the Department of Health & Human Services,<br><br>Defendants. | Civil Action No. 1:15-cv-03588-PAE |

**DECLARATION OF SCOTT GOTTLIEB, M.D. IN SUPPORT OF PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION**

I, SCOTT GOTTLIEB, M.D., declare:

## I. Introduction and Overview of Opinion

1. My name is Dr. Scott Gottlieb. I have been retained by attorneys for Amarin Pharma, Inc. and various individual doctors to provide expert testimony concerning the Food and Drug Administration's ("FDA" or "the agency") drug-labeling process, FDA's policies regarding off-label use and dissemination of information about FDA-approved drugs, and proposed alternative policies related to off-label information that are less speech restrictive than FDA's current practices that virtually ban the dissemination of truthful, non-misleading information concerning the off-label uses of approved drugs.

## II. Background and Qualifications

2. From 2003-2004, I served as a Senior Advisor to FDA Commissioner Mark McClellan and then as FDA's Director of Medical Policy Development. As the agency's Director of Medical Policy Development, I was responsible for, among other matters, coordination of medical policy initiatives between the Office of the Commissioner and each of FDA's medical product centers (the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH)).

3. As Senior Advisor to FDA Commissioner McClellan, I advised the Commissioner with respect to emerging technologies and regulatory policy development in FDA's three medical centers, drafted the Commissioner's speeches, reviewed new guidance documents and regulations, and served as a member of the White House Biodefense Interagency Working Group, among other responsibilities. Among the initiatives I worked on related to the FDA's labeling policies was its new framework for enabling qualified health claims to be incorporated into food labels.

4. I left my positions at FDA in 2004, to serve as a Senior Advisor to the Administrator of the Centers for Medicare and Medicaid Services (CMS) in 2004. In this role, I helped direct the implementation of new regulations for the Medicare Part D drug benefit and supported the agency's policy work on quality improvement, coverage, and payment decision-making—particularly related to prescription drugs and new medical technologies.

5. From 2005-2007, I served as FDA Deputy Commissioner for Medical and Scientific Affairs. In this capacity, I coordinated medical and scientific policy and regulatory

affairs for the Commissioner's office, served as a senior policy advisor to the Commissioner, and handled FDA liaison with federal agencies including the U.S. Department of Health and Human Services, the Drug Enforcement Agency, the Department of Agriculture, and the White House. I also assumed the role of Acting Commissioner during the FDA Commissioner's extended absence and travel and had delegated authority to act as the principal deputy commissioner. Among the regulatory initiatives I worked on as FDA Deputy Commissioner related to FDA's drug labeling policies was the agency's new Physician Labeling Rule, which enabled manufacturers to update and improve product labeling and was the first major revision to the drug labeling regulations in more than a decade; and guidance to update FDA's policy regarding its safe harbor enabling sponsors limited ability to disseminate medical journal article reprints that concerned off-label information about a sponsor's marketed drugs.

6. I have testified 14 times as a witness on health and regulatory matters before the United States Senate and the House of Representatives.

7. Among other honors and awards for my work, I received the FDA Special Recognition Award (2007) and the CMS Administrator's Citation in recognition of leadership, performance, and dedication to the public service and programs of the U.S. Department of Health and Human Services (2004).

8. I received an undergraduate degree in Economics from Wesleyan University (Middletown, Connecticut) in 1994, and a medical degree from the Mount Sinai School of Medicine in 1999. I completed a residency in internal medicine at the Mount Sinai Hospital in New York in 2002, served as an attending physician and Hospitalist at Stamford Hospital from 2003-2010 and an attending physician and a Clinical Assistant Professor of Medicine at New

York University's Tisch Hospital in New York, New York and the New York University School of Medicine from 2011-2014.

9. Besides being a physician, I am a Resident Fellow at the American Enterprise Institute, a nonpartisan, not-for-profit institution dedicated to research and education on issues of government, politics, and economics. My work at AEI focuses on FDA regulatory policy; healthcare reform; and the economic, regulatory, and technological forces driving the transformation of healthcare.

10. I currently serve as an editorial board member to *The Food and Drug Law Institute's Policy Forum*, the publication *Cancer Commons*, and the journal *Value Based Cancer Care*. I am also a member of the policy boards of the Society of Hospitalist Medicine and the Leukemia and Lymphoma Society, and a member of the advisory board to the National Coalition of Cancer Survivorship. In addition, I serve as a board member for several corporate entities, as a venture partner at the venture capital firm New Enterprise Associates, and a partner at T.R. Winston, a healthcare merchant bank that invests in life science companies. My professional experience and background is set forth in Exhibit A.

11. I am being compensated based on the number of hours worked on this matter at a billing rate of $600 per hour. I will also be reimbursed for reasonable expenses. My compensation is not contingent in any way on my opinion or the substance of any testimony in this matter or the outcome of this litigation.

## III. Summary of Opinions

### A. Medically-Recognized, Off-Label Uses Provide Significant Public Health Benefits, as FDA Has Repeatedly Affirmed

12. While framing the substantial interest that FDA has in maintaining its restrictions on access to certain truthful, non-misleading information as a way to advance its regulatory prerogatives and support its existing regulatory framework, Dr. Janet Woodcock acknowledges that there remains a tension between these restrictions on information sharing and public health goals. In her words, this tension is between "the substantial public health interests underlying the premarket review process and other important interests such as furthering scientific research and supporting healthcare provider and patient decision-making for individual patient treatment."[1] While the FDA's regulatory and policy interests are framed at length, the FDA's established public health views regarding the benefits of off-label prescribing and access to information concerning these uses are addressed in limited, if any, detail. FDA officials, including Dr. Woodcock, have on other occasions recognized the public health benefits that accrue when doctors are able to prescribe FDA-approved drugs for medically recognized, but off-label uses and, it follows, to be informed about these uses. Toward these ends, the FDA has supported the ability of doctors to use approved drugs for any medically-recognized indications as part of the practice of medicine. This includes uses that have not been affirmatively approved by the FDA. It is reasonable that if FDA believes that off-label prescribing is an essential part of the practice of medicine, and FDA acknowledges that doctors can and should be, in some circumstances, prescribing approved drugs for off-label uses, then doctors should also be

---

1 Declaration of Dr. Janet Woodcock in *Amarin Pharma, Inc., et al* v. *U.S. Food and Drug Administration*, 15 Civ 3588 (PAE) United States District Court, Southern District of New York (Dkt. 52) (hereafter, the "Woodcock Declaration") at ¶ 25.

adequately informed about the risks and benefits of such uses, and have provided to them any truthful, non-misleading scientific information that can inform these medically recognized uses.

13. The benefits from fostering the off-label use of drugs for medically-recognized indications stems from the high bar that FDA maintains for approving new indications, and the inherent delay between the availability of scientific information that supports important new uses for drugs, and the FDA process for approving new claims related to these indications. The Woodcock Declaration takes note of the fact that FDA maintains a high bar to the approval of new drugs, and new uses for already marketed drugs through a Supplemental New Drug Application (sNDA).[2] The clear benefit of FDA's high bar is that it helps ensure that new drugs are safe and effective for their intended use. It also provides incentives for drug makers to develop additional clinical data that might not otherwise exist, which then becomes available to guide medical practice. While this demanding process provides certain benefits, it also limits the utility of the FDA approval process to the practice of medicine. For instance, the resulting lag between scientific development and FDA approval means that providers are not always able to wait for FDA to approve a new indication and issue new labeling before prescribing a drug for a promising new use. For these and other reasons described in this report, FDA understands that the requirement for FDA-approved labeling does not (and by its nature cannot) regulate or limit a provider's prescribing decisions. In fact, FDA has expressly acknowledged that once a drug receives initial FDA approval, the agency lacks authority to regulate or interfere with a provider's use of that drug, except in certain limited circumstances not relevant here.[3] As a

2 Woodcock Declaration at ¶¶ 35-36.

3 The limited exceptions to the agency's lack of authority to regulate or interfere with the clinical practice of medicine generally involve protection of the public's health, including for example, where a certain use of an FDA-approved drug is known to endanger patients. *E.g.*, 37 Fed. Reg.

result, FDA recognizes that medical providers may prescribe an approved drug for any use, including for "off-label" uses not listed in the FDA-approved labeling.[4] Moreover, the agency recognizes that off-label prescribing is an important clinical practice and provides public health benefits. Consistent with these principles, FDA's policy is "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment," regardless of whether FDA has approved a drug for the specific use that is in question.[5]

14. Additionally, FDA understands that manufacturers do not—and sometimes cannot—seek FDA approval for every new use because of concerns or challenges that may arise in performing the types of clinical trials that FDA generally requires for obtaining formal approval. In some cases, it may be unethical to perform a certain kind of study required to satisfy FDA's requirements. For example, for the purpose of satisfying FDA's clinical trial requirements, it may be impractical or unprincipled to compel patients to randomly receive an inert placebo if the drug being examined is targeted to a serious medical condition and is already widely known to provide some benefit to patients. It also might not be possible to enroll patients in a study where some consumers would be forced to get a placebo when a drug is already available on the market for another indication, and thus accessible to patients outside the confines of the clinical trial that FDA requires. Patients rarely want to risk being randomly

---

16,503, 16,504 (Aug. 15, 1972), or where a drug is approved in conjunction with "Elements to Assure Safe Use" that restrict, in certain ways, how doctors can prescribe a medicine.

[4] *E.g.*, 59 Fed. Reg. 59,820, 59,821, 59,825 (Nov. 18, 1994); *Use of Approved Drugs for Unlabeled Indications*, FDA Drug Bulletin, Vol. 12, No. 1, at 4-5 (April 1982).

[5] FDA, *"Off-Label" and Investigational Use of Marketed Drugs, Biologics, and Medical Devices — Information Sheet* (available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm, last updated Oct. 18, 2010); 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975).

assigned to a placebo when the drug is otherwise freely available to them. For these reasons, certain off-label uses are sometimes not possible to study in any clinical trial construct that would satisfy FDA's high bar. Moreover, scientific developments—and their corresponding effects on the practice of medicine—also indisputably move faster than the FDA review and approval process, even when it is possible to conduct the type of studies that could meet FDA's high standards. In view of these facts, FDA readily admits that "[a]dvances in medical knowledge and practice inevitably precede labeling revision by the manufacturer and formal labeling approval by [FDA]."[6]

15. That the FDA approval process invariably moves much more slowly than scientific development is a function of its design. FDA requires drug makers to demonstrate the safety and efficacy of each new use through a series of clinical trials to obtain approval. Typically, the agency will require the conduct of two, large-scale, prospectively randomized, and well-controlled clinical trials, each demonstrating convincing results on its own and affirming one another.[7] FDA's goal is not only to establish the safety profile a drug, and whether a medicine delivers benefit to patients. The purpose is also to establish with a high degree of statistical precision the complete magnitude of the benefit that a drug is delivering, so that it may be described with mathematical certainty in FDA-approved labeling. To satisfy FDA's standards, manufacturers typically spend years developing clinical data and preparing sNDA submissions to the agency. Further, even where the results of these trials demonstrate that clear evidence exists that a new use is safe and effective, additional time will lapse between FDA's

---

6 *E.g.*, 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975).

7 Food and Drug Administration, Guidance for Industry. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, May 1998, available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf.

receipt of these data and inclusion of the new use in the drug's labeling—6.0 to 15.6 months for priority approvals, and 10 to 22.1 months for standard approvals.[8] Meanwhile, information regarding new uses of already marketed drugs may be readily available through announcements at medical conferences, published reports in medical journals, doctors' own clinical experience with patients, and other sources. By definition, prescribing decisions made solely on the basis of FDA-approved labeling would be made according to evidence that excludes the most up-to-date clinical data, thereby denying patients important opportunities to get access to the latest clinical practice and for doctors to tailor each patient's treatment plans based on the most up-to-date scientific information (information often not reflected in the FDA-approved labeling).[9]

16. For all of these reasons, FDA recognizes that off-label use is a common and often beneficial feature of medical practice.[10] The agency has said that in certain situations, off-label uses or treatment regimens may constitute "a medically recognized standard of care."[11] FDA has repeatedly affirmed that it recognizes off-label prescribing as an important part of medical

---

8 FDA, *Prescription Drug User Fee Act Performance Reports*, 2000-2005 (available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/PDUFA/default.htm).

9 *See* Scott Gottlieb, M.D., FDA Deputy Commissioner for Medical and Scientific Affairs, Speech before Windhover's FDA/CMS Summit ("Gottlieb FDA/CMS Summit Speech") (Dec. 5, 2006) (available at http://www.fda.govinewsevents/speeches/ucm051792.htm). *See, e.g.*, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (recognizing the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information" about off-label uses).

10 *E.g.,* Gottlieb FDA/CMS Summit Speech; 63 Fed. Reg. 31,143, 31,153 (June 8, 1998); *Use of Approved Drugs for Unlabeled Indications*, FDA Drug Bulletin, Vol. 12, No. 1, at 4-5 (April 1982).

11 FDA, *Guidance For Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (Jan. 13, 2009) (available at http://www.fda.gov/oc/op/goodreprint.html); 63 Fed. Reg. 31,143, 31,153 (June 8, 1998); *Washington Legal Found. v. Friedman (WLF I),* 13 F. Supp. 2d 51, 56 (D.D.C. 1998).

practice and "accepted medical practice often includes drug use that is not reflected in the approved drug labeling."[12]

17. For example, the agency has recognized in regulation that after FDA has "judg[ed] the safety and effectiveness of drugs and the truthfulness of their labeling," health care practitioners are "responsible for making the final judgment as to which, if any, of the available drugs" will be prescribed "in the light of the information contained in their labeling and other adequate scientific data available . . . ."[13] More broadly, FDA has said that off-label use of a product can constitute the standard of good medical care, stating, "FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice."[14] On other occasions, FDA has affirmed that patients benefit when providers have access to as much truthful and non-misleading information about the risks and benefits of new drugs, including off-label uses for already approved drugs, as is practical, making note of the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information on important unapproved uses of approved products."[15]

18. Moreover, given the intrinsic limitations of a drug's labeling, FDA understands that providers often do not rely on labeling information in making prescribing decisions for off-label uses. For these reasons, FDA's policy is that providers should consider a drug's labeling to

---

12 *Use of Approved Drugs for Unlabeled Indications*, FDA Drug Bulletin, Vol. 12, No. 1, at 4-5 (April 1982) (recognizing, "[w]ith respect to its role in medical practice, the package insert is informational only").

13 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972).

14 *See*, 63 Fed. Reg. 31,143, 31,153 (June 8, 1998).

15 *See* Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998).

be informational only[16] and also rely upon any other adequate scientific data available to them in making prescribing decisions. Consistent with this approach, FDA has accepted that "the labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice" and "advances in medical knowledge and practice inevitably precede labeling revision."[17]

19. FDA has similarly acknowledged that the standard is different for the drug approval process and for clinical practice, where compendia, expert guidelines, and similar literature guide medical providers. That is particularly relevant in this case, as Vascepa® is a medically-accepted treatment for the treatment of "persistently high triglycerides" (as that term is used in the Complaint) that is supported both by clinical guidelines and compendia listings. It is common in medical practice that clinical decisions must be made in the absence of evidence that meets FDA's exacting standards. More practical standards such as those adopted by compendia and expert guidelines are the basis for many decisions made in clinical practice. As Dr. Woodcock previously stated in a recent interview with *The Pink Sheet*, "How do you generate knowledge that you can rely on? . . . I think there are very different opinions about that in different sectors. The regulators come down on pretty reliable data and inferences because we make decisions that are big regulatory decisions. If you are a payer or an individual practitioner, you make decisions . . . based on other considerations and that is reasonable."[18]

---

16 *Use of Approved Drugs for Unlabeled Indications*, FDA Drug Bulletin, Vol. 12, No. 1, at 4-5 (April 1982).

17 40 Fed. Reg. 15, 392, 15, 394 (Apr. 7, 1975).

18 The Pink Sheet. Drug Developers Facing "Unsettled Period of 5 to 10 Years as CER Environment Evolves, FDA's Woodcock Says." June 28, 2010 (quoting Janet Woodcock).

20. From FDA's acceptance that there are public health benefits attributable to the ability of providers to prescribe drugs for off-label uses, it necessarily follows that the benefits and risks of such prescribing will be better informed and optimized if providers have easier access to more truthful, non-misleading information about these uses. To these ends, FDA has previously said that, in providing the most up-to-date medical care to patients, and prescribing drugs based on the latest scientific information, providers must frequently supplement the information available in FDA-approved labeling. For example, FDA has stated the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information" about off-label uses.[19] Similarly, as FDA's former Associate Commissioner for Health Affairs noted, "The very latest information that can be of value to physicians . . . must be made available as soon as possible. Frequently, unlabeled use information is extremely important."[20] Consistent with these views, FDA has likewise advised providers on multiple occasions that they should rely not only on the information in a product's FDA-approved labeling, but also on any "other adequate scientific data available" to them in making prescribing decisions.[21] Toward these ends, FDA officials have stated that FDA-approved labeling is unavoidably limited because it "cannot be both authoritative and avant-garde."[22]

21. Moreover, Dr. Woodcock has previously recognized that providers want more of this information to be provided by the manufacturer of a particular drug (setting aside the tension

---

[19] *See* 63 Fed. Reg. 64,556, 64,579 (Nov. 20,1998); *see also* 63 Fed. Reg. 31,143, 31,153 (June 8,1998).

[20] Stuart Nightingale, Unlabeled Uses of Approved Drugs, 26 Drug Information 1992. J. 141, 145.

[21] 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972); 68 Fed. Reg. 6,062, 6,071 (Feb. 6, 2003).

[22] Robert Temple, Legal Implications of the Package Insert, 58 Med. Clinics of N. Am. 1151, 1155 (1974).

this creates as a result of the restrictions FDA places on the exchange of this kind of information). Dr. Woodcock stated,

> Because people would like to receive all the latest information on a drug ***from manufacturers***, there has been a lot of debate about uses that are considered 'off-label'—not approved by FDA. Obviously, medical science doesn't happen in spurts, but continuously. After a drug is out on the market, health professionals continuously experiment with new uses. FDA thinks that's appropriate and doesn't want to restrict that kind of use of drugs. But we don't currently permit manufacturers to promote these new uses until it's proven that they work and are safe [through formal FDA review and approval].[23]

22. The ability of doctors to prescribe drugs off-label also supports FDA's regulatory prerogatives, even while — as Dr. Woodcock maintains — the dissemination of information concerning these uses could challenge certain aspects of FDA's regime and its regulatory prerogatives in other ways.[24] For example, when it comes to sNDAs for new uses of FDA-approved drugs, the fact that physicians are free to prescribe drugs off-label provides a measure of relief to FDA and allows the agency to take extra time to resolve questions that might otherwise be peripheral to the core request for supplemental approval. As a result, FDA is generally thought to sometimes review supplemental applications (i.e., applications for approval of additional uses of already-approved drugs) with less urgency than applications for initial approval, precisely because it understands that the drugs are already available to patients and medical providers to prescribe off-label.

---

23 Tamar Nordenberg. Why Should FDA Regulate Drugs. An Interview with Janet Woodcock, M.D., Director of FDA's Center for Drug Evaluation and Research. U.S. Food and Drug Administration (emphasis added).

24 Woodcock Declaration at ¶ 29.

23. Off-label use is especially prominent in the treatment of many cardiac problems.[25] Because of the complexity of cardiac disease, information about medically recognized indications is particularly important for providers to have access to. A 2006 study found that off-label prescribing among office-based medical providers was most common among cardiac medications – forty-six percent of cardiac therapies prescribed in the outpatient setting were for off-label uses.[26] For example, with respect to heart disease, many beta-blockers and angiotensin-converting enzyme ("ACE") inhibitors — widely considered the standard of care in congestive heart failure (CHF) — have never been approved by the FDA to treat CHF.[27] Beta-blockers were actually *contraindicated* by FDA for heart failure patients for many years, until, based on off-label use and further research,[28] they were proven to reduce mortality in these patients.[29] Similarly, other common cardiac therapies considered to be a medically-recognized standard of

---

25 R.S. Stafford and D.C. Radley. The underutilization of cardiac medications of proven benefit, 1990 to 2002. Journal of the American College of Cardiology. 2003;41:56-61.

26 David C. Radley et al., *Off-label prescribing among office-based physicians*, 166 Archives of Internal Medicine, 1021, 1023 (2006).

27 William M. Bennett, *Off-Label Use of Approved Drugs: Therapeutic Opportunity and Challenges*, 15 J. American Society of Nephrology, 830 (2004); Jessup, *supra* note 12, at 2015 (noting that, for "the most frequently prescribed beta-blocker in the United States[,] atenolol[,] there have been no studies to date on [its] use [] in patients with heart failure").

28 L.D. Fisher. Carvedilol and the Food and Drug Administration (FDA) approval process: the FDA paradigm and reflections on hypothesis testing. Controlled Clinical Trials. 1999 Feb;20(1):16-39.

29 Bennett, *supra* note 16, at 830; G. Michael Felker, *Inotropic therapy for heart failure: An evidence-based approach*, 2001 American Heart Journal, 142, 393-401 ("Over the last decade, the treatment of heart failure has been turned on its head – drugs that were formerly considered contraindicated (β-blockers) are now the standard of care, whereas drugs that were once considered the most promising (positive inotropes) are now known to increase mortality.").

care, such as digoxin, nitroglycerin, and angiotensin-receptor blockers are routinely used off-label for treatment of certain heart patients.[30]

### B. Numerous, Viable, Less Speech-Restrictive Alternatives Exist to FDA's Near-Total Ban on Off-Label Promotion

24. In my opinion, there are numerous less speech-restrictive alternatives to FDA's current regime — which virtually bans off-label promotion — that would promote FDA's public health goals even better than the current regime does. These alternatives preserve FDA's need to maintain incentives for sponsors to seek supplemental approval for new indications, furnish providers with safeguards that help to ensure the accuracy of scientific information, and are far less restrictive of speech than FDA's current approach, helping to assure that medical providers are better informed of the most up-to-date scientific information. Among these alternatives are frameworks already in common use in healthcare, including: (1) reliance on commercial restrictions on reimbursement for certain off-label uses not supported by sufficient evidence; (2) use of compendia that rank various off-label uses based on the strength of available evidence and assist providers and payors with prescribing and coverage decisions; (3) counter-detailing to educate providers about how to evaluate information on off-label uses; (4) prohibitions or contraindications on those off-label uses that raise more significant public health concerns; and (5) disclaimers to help providers distinguish between the strength of evidence supporting certain uses of drugs. In my opinion, each of these alternatives is a viable, pragmatic approach that can be applied in the real world.

---

[30] Bennett, *supra* note 16, at 830.

**Reliance on Payor Restrictions on Certain Off-Label Uses**

25. One way of encouraging fully-informed decisions about beneficial off-label uses and discouraging potentially harmful off-label uses is to use commercial actors and government payors to establish limitations on the reimbursement of drugs prescribed for all or certain off-label uses. This includes efforts to have the government limit its Medicare and Medicaid reimbursement for certain unapproved uses. The Woodcock Declaration dismisses these approaches, arguing that such an alternative is "impractical to administer and enforce" and would be overly restrictive relative to the status quo.[31] Yet, as a practical matter, elements of this proposed alternative already exist in public and private health insurance programs, are real-world practices, are already supported by substantial government efforts, and can be expanded upon to provide a less speech-restrictive alternative to FDA's current approach. Such restrictions on the reimbursement of off-label prescriptions are already widespread in commercial and government health plans. In 2009, 34 third-party payors that administered the health benefits for one quarter of Medicare and Medicaid beneficiaries nationwide were surveyed regarding practices in off-label reimbursement. About 25% of these payors refused payment for off-label therapy of any kind. Of those who reimbursed off-label therapy, payors said that they imposed restrictions on what they would reimburse in 85% of the cases.[32] The kinds of prohibitions and restrictions that the Woodcock Declaration argues are not a practical alternative to FDA's regime are now common throughout the government and commercial markets. Application of these kinds of restrictions and controls already provides a practical and efficient way of encouraging potentially

31 Woodcock Declaration at ¶ 44.

32 J. Cohen, A. Wilson, and L. Faden. Off-label use reimbursement. Food Drug Law Journal 2009;64:391-403.

beneficial off-label uses and discouraging potentially harmful ones, while not resorting to more intrusive restrictions on truthful speech as a way to achieve these policy goals.

**Reliance on Compendia That Evaluate Off-Label Uses**

26. Another viable, less speech-restrictive alternative to FDA's current approach is to use medical compendia to evaluate off-label uses. In the case of government programs, Medicare and Medicaid already routinely differentiate among different off-label uses of approved drugs, to make judgments about which uses are supported by sufficient evidence to warrant reimbursement under federal programs. (Notably, Vascepa® is listed in recognized compendia for the off-label use at issue in this case.) The Medicare program uses three drug compendia, which are private publications — supported by panels of expert clinical and scientific thought leaders — whose mission is to evaluate the level of evidence available to substantiate different off-label uses of approved cancer drugs and make recommendations about which off-label uses encompass a "medically-accepted indication." The Centers for Medicare and Medicaid Services (CMS) will typically only reimburse for the off-label use of cancer drugs when the drugs are supported by a certain level of evidence, as determined by one of these three compendia. The compendia system is not the only tool that CMS uses to restrict access to certain off-label uses of drugs when the supportive data is judged to be insufficient. If an off-label use is not included in one of these compendia, then Medicare contractors are permitted to rely on peer-reviewed research published in one of 26 specified journals[33] in formulating their own policies as to whether to cover these uses. This process also includes some absolute prohibitions on reimbursement of certain off-label uses. Under the current approach adopted by

---

33 Recent Developments in Medicare Coverage of Off-Label Cancer Therapies. Journal of Oncology Practice 2009 vol. 5 no. 1 18-20.

CMS, if any of the recognized compendia include a "Not Recommended" listing for a particular off-label use, then that use is not eligible for any coverage; even if the same use is deemed acceptable in one of the other compendia. Off-label uses that CMS deems medically inappropriate (published, for example, in a Medicare National Coverage Determination) are also not eligible for coverage, even if support exists in one of the compendia. This is consistent with the prohibitions on off-label prescribing that the Plaintiffs put forward as another less speech-restrictive alternative to FDA's current regime.

27. These policies are directed in statute and defined in regulation. In creating these constructs, Congress has recognized that certain off-label prescribing is appropriate for delivering high quality and effective patient care. In several situations, Congress has mandated that payors in federal health care programs must provide reimbursement for off-label uses that are "medically accepted" and may reimburse for other off-label treatments.[34] In one of these instances, Congress enabled Medicare Part D drug plans to cover drugs prescribed for off-label use if the drugs are identified as appropriate for that use in one of three officially recognized drug compendia.[35] Another one of these occasions was the 1993 Omnibus Budget Reconciliation Act,[36] which mandated that Medicare provide coverage for off-label uses of drugs in anticancer chemotherapy regimens if designated compendia supported those uses. This framework was substantially revised as recently as 2008 with the addition of new compendia to Medicare's recognized list, to replace compendia that had ceased publication – thus re-affirming the utility

[34] 42 U.S.C. §§ 1396r- 8(d)(1 )(8)(i), (k)(6), (g)(1 )(8)(i).

[35] 42 U.S.C. §1395w-102(e)(4)(B).

[36] Omnibus Budget Reconciliation Act of 1993, available at https://www.congress.gov/bill/103rd-congress/house-bill/2264.

of this process, and the government's reliance on this mechanism as a way to regulate its reimbursement of certain off-label prescribing, and to restrict access to certain off-label uses where there's a view that a particular medical indication is not supported by sufficient scientific evidence.

28. The compendia are one process for enabling the evaluation of the quality of scientific evidence supporting each particular off-label use. To address FDA's stated concerns about inappropriate prescribing that the agency fears would flow from the more fluid exchange of truthful, non-misleading information about off-label uses, the CMS framework could provide a viable and wholesale alternative to the FDA's broad restrictions on speech. One can even envision FDA playing a role in the compendia process to help advise on the interpretation of science and the application of proper disclaimers to inform providers about the weight of evidence. Instead of maintaining its overly-restrictive policies on speech as a way to coerce compliance with its existing sNDA process, FDA could collaborate with the compendia process. FDA's participation could serve as a way to balance the agency's desire to create incentives for sponsors to seek an sNDA, while still enabling the sharing of medically important and constitutionally protected information, all the while ensuring that there exists a framework to evaluate and rate the strength of the scientific evidence. FDA could also adopt a similar construct to the compendia, and conduct its own evaluations of evidence supporting different off-label uses. A precedent for such an FDA construct already exists, as I will note later.

29. The compendia process enables real-time scrutiny of off-label prescribing, and for this reason, it is relied upon by CMS as a way to differentiate between medically-appropriate off-label uses of cancer drugs. Under this process, the off-label use that is under consideration must be substantiated by a threshold level of evidence that supports the benefits of the proposed use of

the drug relative to its understood risks. A descriptive term or score that is assigned to each proposed use by each compendium typically represents this. These ratings are based on each compendium's evaluation of the available evidence. For example, the American Hospital Formulary Service Drug Information (AHFS-DI) will say whether an indication is supportive. The NCCN Drugs and Biologics Compendium will assign proposed off-label uses to different categories, and CMS will only reimburse for proposed uses rated as being supported by Category 1 or 2A (NCCN's rating for the highest levels of evidence). Micromedex® DrugDex® maintains a similar classification process, and in this case, CMS will only reimburse for indications rated as supported by evidence that meets the compendia's Class I, Class IIa, or Class IIb. To reach these conclusions, the compendia maintain expert staff and advisory committees to assist in evaluating the evidence and the generation of these ratings. For example, the NCCN maintains a network of more than two dozen leading U.S. cancer hospitals, as well affiliations with cancer centers internationally. NCCN draws from this membership to constitute dozens of standing advisory committees comprised of thought leaders in different fields of oncology. These experts meet and speak regularly throughout the year[37] to evaluate new scientific evidence and adjust the medically accepted uses listed in the NCCN compendia (and the classifications that the NCCN assigns to each of these uses) based on each expert committee's continuous evaluations of the most up-to-date scientific evidence.

30. This entire process has a far ranging impact on clinical practice, does not foreclose medically-beneficial off-label use, and is not confined to government programs. The process also preserves the incentive for sponsors to seek sNDA approval, since such approval

[37] A complete list of the NCCN panel meetings for 2015 is available at http://www.nccn.org/about/meeting_schedule.aspx.

confers higher recognition in the compendia. The compendia process achieves these ends while not seeking to restrict speech, as is FDA's current approach. This compendia process has an impact well beyond government programs, notwithstanding the concerns raised in the Woodcock Declaration that such remedies would only affect federal payors. Surveys demonstrate that through this government-sanctioned compendia process, "Medicare and Medicaid set the pace in terms of specific policies on off-label use reimbursement, particularly with regard to anti-cancer agents and biologics."[38] Private payors readily benchmark their own reimbursement and coverage decisions to this government process, magnifying its impact and creating a uniform standard for off-label prescribing based on a consistent and thorough evaluation of the available science. Private payors will often tailor their coverage policies to make certain reimbursement either more expansive, or in other cases, restrictive. For example, the policy of Emblem Health, just to take one example, states that a "medically accepted indication" that the payor will reimburse is any "usage consistent with FDA-approved indication (labeled indication);" or "Articles or Local Coverage Determinations (LCDs) published by National Government Services;" and "Usage supported by ≥1 citations in at least 1 of the… drug compendia" that are recognized by CMS.[39] To take another example, UnitedHealthcare's policy is to follow the recommendations made by a single publication, the NCCN compendium. This is consistent with recent surveys of payors. About 70% of payors surveyed utilize compendia to assist with coverage decisions for oncology indications when a drug or biologic is not already approved by FDA for a specific indication (in the latter case, coverage is usually automatic). Of the four main

---

38 J. Cohen, A. Wilson, and L. Faden. Off-Label Use Reimbursement. Food Drug Law Journal, 2009;64(2):391-403.

39 Coverage policies of Emblem Health, available at http://www.emblemhealth.com/~/media/Files/PDF/_med_guidelines/MG_Off_Label_FDA_Approved.pdf.

compendia recognized by government payors like Medicare, the private payors stated that they most often reference NCCN and AHFS-DI when making a coverage decision.[40]

31. This entire process is not unique to cancer drugs – although the off-label prescribing of cancer drugs is one place where the Medicare program has already used compendia as a way to regulate reimbursement for, and therefore access to, off-label prescribing. Similar compendia are maintained for other clinical fields of medical practice, including cardiology. If these compendia were to serve as an alternative to FDA's restrictions on speech, which is the agency's current method of achieving its stated public health goals, then it is reasonable to assume that the compendia process itself could be expanded and augmented with additional conditions to safeguard its integrity, if such a framework were to become an even more integral part of the federal regulatory scheme. For example, compendia recognized by FDA for purposes of sanctioning the sharing of information around certain off-label uses and providing proper disclaimers to these indications might have to meet certain criteria for how they assess information and manage potential conflicts of interest. Many of the compendia already have adopted these principles as part of their participation in the CMS framework, and they already have carefully considered rules in place to govern the reliability of their processes.

32. These frameworks maintain incentives for the submission of an sNDA — one of the principle concerns raised in the Woodcock Declaration[41] — since approved uses of drugs are almost always granted some level of coverage, while off-label uses must often undergo further scrutiny and can face limited or fully restricted coverage by these compendia processes. The

---

40 http://www.xcenda.com/Insights-Library/Payer-Perspectives/Payer-Perspectives-on-the-Role-of-Compendia-in-Patient-Access/.

41 Woodcock Declaration at ¶ 36.

ability to gain more unfettered access to coverage under Medicare and private payors provides a powerful incentive for manufactures to seek FDA approval for off-label uses of new drugs. In general, the likelihood that a particular off-label use will be reimbursed can be thought of as a continuum in which FDA-approved use has the highest probability of reimbursement; mentions of an off-label use in society guidelines, compendia, or peer-reviewed literature are less likely to be reimbursed, and expert opinions of off-label use, including data presented in non-peer reviewed abstract form, being least likely to be reimbursed.[42] Moreover, it is becoming easier for payors to regulate off-label prescribing. Federally imposed and commercial restrictions on coverage for off-label uses not medically recognized are becoming more common and easier to implement. Even where compendia are not used to benchmark coverage policies, payors are more actively scrutinizing the indications for which drugs are prescribed and denying reimbursement in certain cases where off-label uses of drugs are not medically recognized. Electronic prescribing platforms are rendering such procedures more feasible by making it easier for payors to see the indication for which a drug is being prescribed. This, in turn, makes it easier for payors to restrict reimbursement based on a payor's (or compendia's) assessment of the science supporting a particular use. The ability to gain formal FDA approval for a new use of an already approved drug, and thus earn FDA's permission to disseminate information about that indication, is not the only, and indeed will be a diminishing, incentive to file an sNDA with FDA. The need to gain preferred coverage status on compendia and drug formularies is an increasingly profound commercial reason to seek an sNDA, especially as these marketplace tools and procedures continue to take a more prominent role in regulating prescribing decisions made by medical providers.

---

[42] A. Aronsohn, N. Reau, and D. Jensen. Preparing for the Uncertain Yet Inevitable: Off-Label Combinations of Antiviral Agents in Hepatitis C Virus. Hepatology, 2013.

**Counter Detailing To Educate Medical Providers on Interpreting Off-Label Information**

33. There are already government efforts underway to actively inform doctors about off-label information. These efforts are consistent with another proposed alternative to FDA's virtual ban on off-label promotion — to educate doctors to recognize false or misleading information. This alternative is far less restrictive of speech than FDA's current approach. The Woodcock Declaration dismisses the practicality of this alternate approach, noting, "It is unrealistic to suggest that this type of program can be conducted on the scale necessary to effectively combat the adverse impact of false and misleading promotion." Yet, the fact that it is already operative and supported by generous government resources validates its feasibility. Toward these ends, the American Recovery and Reinvestment Act earmarked $300 million for the Agency for Healthcare Research and Quality (AHRQ) to conduct an "Academic Detailing Initiative," where the U.S. government funds the equivalent of pharmaceuticals sales reps to visit doctors' offices and inform them about value-based uses of drugs, including off-label uses. Academic detailing "is designed to counter detailing by pharmaceutical and device manufacturers, which critics contend can be biased because of commercial interests."[43] The expressed intent of this federal effort is to counter detail providers in an effort to inform them of the government's view of prescribing decisions, including the off-label uses of drugs.

**Prohibiting or Contraindicating Certain Concerning Off-Label Uses**

34. Other viable, less speech-restrictive alternatives to FDA's restrictions on the dissemination of truthful, non-misleading information abound. FDA could prohibit certain

---

43 AHRQ National Resource Center for Academic Detailing, November 3, 2011, available at http://www.policymed.com/2011/11/ahrq-national-resource-center-for-academic-detailing.html.

unapproved, off-label uses judged to be exceptionally concerning by the agency, or develop tiers based on the level of evidence of benefit or risk with greater regulatory controls applied to products and off-label uses that create the most significant concerns or are substantiated by less evidence. The Woodcock Declaration rejects these kinds of constructs, painting a binary assumption that such a framework would limit all off-label prescribing. It is easy, however, to envision such an approach being implemented in a way that titrates the scope of the restrictions to the level of concern FDA has about a particular use. Among other things, the Woodcock Declaration argues that such a regime would require the "generation of data regarding product dangers before any controls can be applied. It would essentially allow a product to be distributed for unapproved uses without the development of data to support such use and without the submission of the data to FDA." Under this conception of such a scheme, as offered by FDA, a drug could be widely marketed for off-label uses but for the affirmative actions of FDA to demonstrate that such a use is unsafe. In this way, the Declaration argues, "it would therefore return drug regulation to the era before the 1962 amendments, when the government was limited to using post-marketing remedies after the product had injured members of the public at large."[44] However, there is also ample precedent for FDA establishing prospective regimes that evaluate the strength of the available evidence supporting different health claims, and using these evaluations to prospectively rate the evidence and place certain conditions and limits on the dissemination of information based on the agency's ratings.

---

[44] Woodcock Declaration at ¶ 46.

**Disclaimers to Inform Providers of the Strength of the Evidence Supporting Off-Label Uses**

35. This approach, using disclaimers to inform providers of the strength of evidence supporting particular off-label uses, would be far less restrictive of speech than FDA's current practices. It could include the use of regulated disclaimers to appropriately inform providers about the strength of evidence that supports a particular off-label claim. One place where FDA developed a similar framework was its approach to enabling qualified health claims to be placed on food product labels. FDA created a process for systematically evaluating and ranking the weight of scientific evidence relevant to a food substance and disease relationship that was the subject of a qualified health claim. Different levels of scientific evidence resulted in different qualifying language for a claim. To make the system easier for consumers to recognize on food product labels, these disclaimers corresponded to letter grades of "A" through "C" depending on the strength of the evidence supporting a claim. The qualifying language provided by FDA served as a basic template, but it could vary depending on the specific circumstances of each food and disease relationship.[45]

36. A similar regime could also be used to prospectively restrict or greatly limit access to certain off-label uses by contra-indicating them or informing providers when the strength of the evidence supporting a particular use is weak. Absent evidence to support a particular use (and especially in the setting of concerns about safety), FDA could simply contra-indicate the use in its approved labeling, much like it did with qualified health claims on food substances. In other cases, where FDA judges the scientific information supporting a particular use to be insufficient or inadequate to form a complete judgment, but does not judge the

---

45 *See* FDA, Questions and Answers: Qualified Health Claims in Food Labeling, available at http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/ucm207974.htm.

proposed use to be medically inappropriate, the agency could require information about such use to be properly disclaimed in any marketing material. FDA already uses disclaimers in the drug context to qualify unapproved claims. Manufacturers who want to incorporate new efficacy claims about old drugs that never went through the formal FDA approval process (so-called DESI drugs) must include disclaimers noting, among other things, that FDA never approved the claims.[46] FDA's previous approach to enabling qualified health claims to be made on food labels, following the agency's legal setbacks in the *Pearson* litigation,[47] also provides ample precedent for how such a framework might work. A similar construct could be adapted to apply to new uses of already approved drugs.

37. Another alternative remedy put forward by Plaintiffs is for sponsors to submit all potential off-label indications as part of its initial pre-market application. The Woodcock Declaration dismisses this alternative, arguing among other things, "science is currently not capable of divining all potential uses of a medical product from an initial study; data and information develop over time through scientific study before and after product approval."[48] But it is wholly practical for FDA to require sponsors to maintain an up-to-date list of the off-label applications of drugs that sponsors are studying through follow-on research, or observing

---

46 21 CFR 201.200. See especially subsection (c); "Therefore, after publication in the Federal Register of a Drug Efficacy Study Implementation notice on a prescription drug, unless exempted or otherwise provided for in the notice, all package labeling (other than the immediate container or carton label, unless such labeling contains information required by 201.100(c)(1) in lieu of a package insert), promotional labeling, and advertisements shall include, as part of the information for practitioners under which the drug can be safely and effectively used, an appropriate qualification of all claims evaluated as other than 'effective' by a panel of the National Academy of Sciences--National Research Council, Drug Efficacy Study Group, if such claims continue to be included in either the labeling or advertisements."

47 *See Pearson* v. *Shalala*, 164 F.3d 650 (D.C. Cir. 1999).

48 Woodcock Declaration at ¶ 47.

through their interactions with providers. Some of this information is already contained in annual reports that drug makers are required to file with FDA, and is already routinely evaluated by the agency. One can envision such a requirement being used to help support other proposed alternatives that the Plaintiffs put forward. For example, FDA could use this serial list of proposed and observed off-label uses to evaluate for those off-label uses that it seeks to contraindicate in labeling because of specific concerns around the risk and benefit balance. If FDA judges a particular off-label use to be medically accepted, the agency could require sponsors to maintain disclaimers concerning those uses and to incorporate these disclaimers into any promotional material. The disclaimers would inform providers about FDA's views on the weight of scientific evidence supporting a particular off-label indication, similar to the construct applied by FDA to qualified health claims made on food substances.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct to the best of my knowledge, information, and belief, and that this Declaration was executed on June 30, 2015.

______________________________

Scott Gottlieb, M.D.